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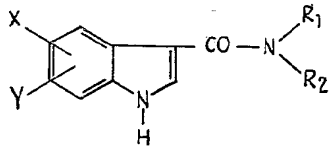
(54) INDOLE CARBOXYLIC ACID DERIVATIVES

(71) We, AGENCE NATIONALE DE VALORISATION DE LA RECHERCHE, a French body corporate of 5 rue Bellini Puteaux, Hauts de Seine, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

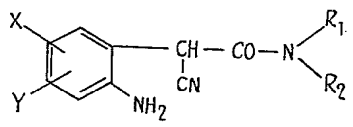
This invention relates to a new process for the production of indole 3-carboxylic acid derivatives and to new derivatives obtainable by this process.

According to the present invention there is provided a process for the production of indole 3-carboxylic acid derivatives of the formula I:—



I

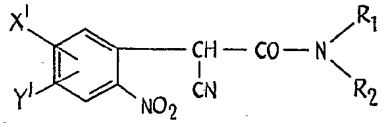
wherein R_1 and R_2 taken separately are the same or different and are hydrogen atoms or substituted or unsubstituted alkyl, aralkyl or aryl groups, and taken together with the nitrogen atom to which they are linked form a 5,6 or 7-membered heterocyclic ring system which optionally may include a second hetero atom, e.g. a nitrogen atom, and X and Y are the same or different and represent hydrogen atoms or halogen atoms, or alkyl or alkoxy groups of 1 to 5 carbon atoms, aralkoxy groups, trifluoromethyl, hydroxyl or amino groups or carboxylic or sulphonic acid groups or their functional derivatives, the said process comprising subjecting to hydrogenolysis a 2-(2 - aminophenyl) - 2 - cyanoacetic acid derivative of the formula III:—



III

where the symbols have the meanings assigned to them above.

In carrying out the aforesaid process a compound of the formula II:—



II

wherein R_1 and R_2 have the meanings assigned to them above, and X^1 and Y^1 have the values assigned to X and Y above but may also represent nitro, is reduced to give, as intermediate, a compound of formula III. This intermediate need not be isolated but may be subjected directly to hydrogenolysis to yield a component of formula I, with loss of ammonia.

When, in the compound II, X^1 or Y^1 represents either NO_2 or an aralkoxy radical these

[Price 25p]

may be modified in course of the hydrogenolysis to give, respectively, an amino or hydroxyl group. If X^1 and Y^1 is a halogen atom this may become replaced by hydrogen.

The reduction may be effected by the use of hydrogen in the presence of a hydrogenation catalyst. It is then possible to arrest the reaction at the stage when the intermediate III is formed by working at a temperature below 50°C. Then, by continuing the hydrogenation at 50 to 150°C the hydrogenolysis of III is induced, leading to the final reduction product I. The nitro-aryl-cyanoacetic acid derivative II may alternatively be reduced by a reducing agent, preferably a ferrous salt but in this case the resultant amino-aryl-cyanoacetic acid derivative III is subjected to hydrogenolysis by means of hydrogen in the presence of a hydrogenation catalyst.

Among the compounds of formula II employed as intermediates for the synthesis of compounds I are compounds which are new *per se*. These include the dimethylamides of the following acids:

2-(2-nitrophenyl)	—	2-cyanoacetic acid
2-(2-nitro-4-chloro-phenyl)	—	„ „ „
2-(2-nitro-6-chloro-phenyl)	—	„ „ „
2-(2-nitro-4-trifluoromethyl-phenyl)	—	„ „ „
2-(2-nitro-4-methyl-phenyl)	—	„ „ „
2-(2-nitro-4-methoxy-phenyl)-	—	„ „ „
2-(2-nitro-6-methoxy-phenyl)	—	„ „ „
2-(2,4-dinitro-phenyl)	—	„ „ „
2-(2,6-dinitro phenyl)	—	„ „ „
2-(2-nitro-4-dimethylsulphamoyl-phenyl)	—	„ „ „

the pyrrolidide, piperidide and 4 - methyl-piperazide (and its hydrochloride) of 2 - (2-nitrophenyl) -2 - cyanoacetic acid, the anilide of 2 - (2 - nitro - 4 - trifluoromethyl - phenyl)-2 - cyanoacetic acid, the 1 - methyl - 4 - piperazide of 2 - (2 - nitro - 4 - chloro - phenyl)-2 - cyanoacetic acid, and the 1 - methyl - 4-piperazide of 2 - (2 - nitro - 4 - trifluoromethyl - phenyl) - 2 - cyanoacetic acid (and its hydrochloride).

The dimethyl amide of the 2 - (2 - amino-phenyl) - 2 - cyanoacetic acid is also a new compound.

According to a further feature of the present invention there are provided, as new chemical compounds, the compounds of formula I set forth above and where the symbols have the values there assigned but with the further proviso that X and Y may not both be hydrogen except when R_1 and R_2 taken together represent a group of the formula $-(CH_2)_n-$ wherein n is an integer from 4 to 6.

Included, therefore, as new products according to the present invention are the dimethylamides of

6-trifluoromethyl —	indole-3-carboxylic acid	
6-methyl —	„ „ „	„
6-methoxy-	„ „ „	„
6-amino	„ „ „	„
6-dimethylsulphamoyl	„ „ „	„

the pyrrolidide and piperidide of indole-3-carboxylic acid, and the anilide and 4-methylpiperazide of 6 - trifluoromethylindole - 3-carboxylic acid.

The new indole derivatives are useful herbicides and may also be used as intermediates in the synthesis of other compounds. Some of the compounds exhibit valuable properties rendering them of use in therapeutics. In particular, for example, the compounds of Examples 10—16, which follow, have been found to possess ocytocic and anaesthetic properties and properties also rendering them useful as anti-inflammatory, hypotensive and tranquillising agents. For such therapeutic purposes they may be converted into the commonly employed dosage forms, e.g. as tablets, solutions, dragees, capsules and suppositories and will generally be used in the form of compositions containing the active substance together with a pharmaceutically acceptable solid or liquid diluent.

When used as herbicides, or as suspensions for any purpose, the compounds are preferably used in association with dispersing or spreading agents which are surface active compounds.

The following Examples will serve to illustrate the invention. The temperatures given are in degrees centigrade.

Example I

Indole-3-carboxylic acid dimethylamide

A. The compound 2 -(2 - nitrophenyl) - 2-cyanoacetic acid dimethylamide (17.5g : 0.075 mol) in 400 ml of ethyl acetate is hydrogenated in the presence of 8 g of a catalyst comprising palladium on a carbon support (the palladium constituting 10% of the catalyst), under a hydrogen pressure of 50 atmospheres, at ambient temperature for 30 minutes and then at 80°C for 4 hours. The product is filtered hot to separate the catalyst, the filtered material being washed with hot dimethylformamied and the combined filtrates are evaporated *in vacuo*. The crude product is recrystallised from methanol. There is then obtained 6.2 g (yield 44%) of the desired amide in a pure condition. M.Pt. 236°.

The dimethylamide used as starting material is prepared as follows:

To 24 g (1 mol) sodium hydride in 150 ml of dimethylformamide there is added slowly, with stirring, at a temperature below 50°, a solution of 59 g. (0.52 mol) of 2-cyanoacetic acid dimethylamide (Bowman and Cavalla, J. Chem. Soc. (1954), 1171) in 200 ml of dimethylformamide. There is then added 79 g. (0.5 mol) of 2-nitro chlorobenzene in 200 ml of dimethylformamide and the mixture is stirred at 20° for 15 hours. The product is filtered, the filtrate diluted with 1000 ml of water and acidified with 60 ml of concentrated hydrochloric acid. The amide is thus precipitated quantitatively (M. Pt. 123—124°). By recrystallisation from 150 ml of aqueous methanol there is obtained 95 g (yield 81%) of the pure product melting of 125—126°.

B. Preparation in two stages

The compound 2 - (2 - nitrophenyl) - 2-cyanoacetic acid dimethylamide (58.g; 0.25 mol) in 200 ml of ethyl acetate is hydrogenated in the presence of 6 g. of palladised carbon, at a hydrogen pressure of 50 atmospheres for 30 minutes at ambient temperature.

After filtering off the catalyst the filtrate is cooled to 0°; there is thus precipitated 0.5 g of indole 3-carboxylic acid dimethylamide. After separating this, the solution is evaporated and then is obtained quantitatively the crude 2 - (2 - aminophenyl) - 2 - cyanoacetic acid dimethylamide (m. pt. 110—112°). By recrystallisation from 25 ml of methanol 39 g of the pure product (77% yield) was obtained, melting at 114°.

The foregoing product (20:3 g; 0.1 mol) in 150 ml of dimethylformamide was hydrogenated in the presence of 4 g of palladium carbon (10% palladium) at a pressure of hydrogen of 50 atmospheres, for 5 hours at 80°. The product is filtered hot to separate the catalyst. By cooling the filtrate a proportion of the indole carboxamide crystallised. After separating this, the filtrate was evaporated in vacuo to obtain a further quantity of the amide. By recrystallising the crude product from methanol there was obtained 14.3 g (yield 76%) of the pure amide melting at 236°.

C. Preparation by hydrogenolysis of an intermediate halogenated compound.

The compound 2 - (2 - nitro - 4 - chlorophenyl) - 2 -cyanoacetic acid dimethylamide (26.7 g; 0.1 mol) in 150 ml of dimethylformamide was hydrogenated in the presence of 5.4 g of palladised carbon (10% palladium) at a hydrogen pressure of 50 atmospheres for 1 hour at ambient temperature and then for 5 hours at 80°. The product is filtered hot to separate the catalyst. By cooling the filtrate there was obtained 5.9 g of crystals of the pure indolecarbamate. By addition of water to the mother solution a further quantity (5.3 g.) of the pure amide is obtained (total yield 50%), M.Pt. 236°.

The dimethylamide used as starting material may be obtained as follows:—

To a suspension of 9.8 g (0.4 mol) of sodium hydride in 150 ml of dimethylformamide there is added slowly, with stirring, at a temperature below 50°, in a current of nitrogen, a solution of 22.7 g (0.2 mol) of 2-cyanoacetic acid dimethylamide in 150 ml of dimethylformamide. There is then added 38.5 g (0.2 mol) of 2,5-dichloronitrobenzene and the mixture is stirred at 20° for 18 hours. After filtration, the filtrate is diluted with 800 ml water and acidified with 25 ml of concentrated hydrochloric acid. There is thus precipitated 51.6 g (yield 95%) of amide melting at 122—124°. By crystallisation from methanol there

is obtained 44 g (yield 82%) of the pure amide, M.Pt. 124—125°.

Example 2
6-methoxyindole-3-carboxylic acid dimethylamide

The compound 2 - (2 - nitro - 4 - methoxyphenyl) - 2 - cyanoacetic acid dimethylamide (13.15 g; 0.05 mol) in 100 ml of dimethylformamide was hydrogenated in the presence of 2.5 g of palladised carbon (10% palladium) at a hydrogen pressure of 50 atmospheres first at ambient temperature for about half a hour and then at 75° for 3 hours. The product is filtered hot to separate the catalyst and the filtrate is cooled to induce crystallisation of the indolecarboxamide. By evaporation of the mother liquid a further quantity of the product is obtained, which is recrystallised from dimethylformamide.

There is thus obtained a total of 6.8 g (yield 62%) of the pure product, melting at 270° (No change in melting point was obtained on a sample which had been re-recrystallised from dimethylformamide).

The dimethylamide used as starting material may be obtained as follows: —

To a suspension of 9.6 g (0.4 mol) of sodium hydride in 200 ml hexamethylphosphoramide (HMPT) is added, little by little, at a temperature below 50°, under a current of nitrogen, while stirring, a solution of 25 g (0.225 mol) of 2-cyanoacetic acid dimethylamide (prepared by the method of Bowman and Cavalla, J. Chem. Soc. (1954), 1171) in 100 ml of HMPT. There is slowly added to the product obtained a solution of 37.5 (0.2 mol) of 2-nitro - 4 - methoxychlorobenzene in 100 ml of HMPT while maintaining the temperature at 50° and stirring. The mixture is maintained at this temperature for 4 hours and the product is then filtered, the filtrate diluted with 800 ml water and acidified with 20 ml of concentrated hydrochloric acid to precipitate the amide formed. After cooling to 0° the solid is separated, washed with water and dried. There is thus obtained 47.5 g (yield 90%) of product melting at 90—91°. By recrystallisation from methanol the pure amide is obtained, M.Pt.94°.

Example 3
6-aminoindole-3-carboxylic acid dimethylamide

The compound 2 - (2,4 - dinitrophenyl) - 2-cyanoacetic acid dimethylamide, in 150 ml of dimethylformamide is hydrogenated in the presence of 2 g. of palladised carbon (10% palladium), at a pressure of 50 atmospheres first at ambient temperature for 45 minutes and then at 80° for 2 hours. After filtering hot to remove the catalyst and evaporating down the filtrate the crystallisation of the residue was induced by trituration with a little methanol. On recrystallising the solid product from 30 ml of methoxyethanol there was obtained 4 g (yield 40%) of pure product melting at 260°.

The dimethylamide used as starting material may be prepared as follows: —

To 4.8 g (0.2 mol) of sodium hydride is 100 ml of dimethylformamide, there are added slowly, with stirring, a solution of 12.3 g (0.11 mol) of 2-cyanoacetic acid dimethylformamide. To the solution of the sodium derivative obtained there was added, little by little, with cooling to 15—20°, a solution of 20.5 g (0.1 mol) of 2,4 - dinitrochlorobenzene in 60 ml of dimethylformamide. After stirring the mixture at 20° for 3 hours, it was filtered, the filtrate diluted with 450 ml water and acidified with 12 ml of concentrated hydrochloric acid. The amide thus precipitated is separated, washed with water and dried. The amide is thus obtained quantitatively in a pure condition, melting at 161°; (its melting point is unchanged after recrystallisation from acetone).

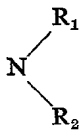
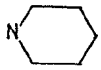
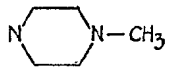
Example 4
6-trifluoromethylindole-3-carboxylic acid anilide

The compound 2 - (2 - nitro - 4- trifluoromethylphenyl) - 2 - cyanoacetanilide (10 g; 0.029 mol) in 150 ml of dimethylformamide was hydrogenated under a pressure of 50 atmospheres, in the presence of 2.5 g of palladised carbon (10% palladium) at ambient temperature for 1 hour and then at 80° for 8 hours. After hot filtering to remove the catalyst, the filtrate is evaporated under vacuum and the residue recrystallised from methanol. There is obtained 4.3 g (yield 50%) of the required product: it is pure and melts at 224°.

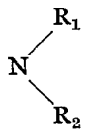
The anilide used as starting material is obtained as follows: The required sodium derivative is obtained from 8 g (0.05 mol) of 2-cyanoacetanilide (M.Pt. 198—200) and 2.4 g (0.1 mol) of sodium hydride of 100 ml of dimethylformamide. There is then added slowly, with cooling, a solution of 11.25 g 0.05 mol) of 2 - nitro - 4 - trifluoromethylchlorobenzene in 25 ml of dimethylformamide. The mixture is stirred at 20° for 4 hours, filtered and the filtrate diluted with 400 ml water. By addition to the resulting solution of 10 ml concentrated hydrochloric acid the amide formed is precipitated. It is dried and recrystallised from 80 ml of methanol: 15 g (yield 85%) of the required pure product is obtained, melting at 182°.

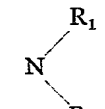
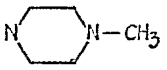
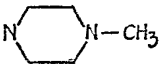
Examples 5 to 10

By operating in a similar manner the compounds in the following table, identified by the value of the symbols with reference to formula I, are obtained. The symbol DMF is used for dimethylformamide.

Ex.		X	Y	melting point (solvent of re-crystallisation)	Yield
5	$N(CH_3)_2$	6—CF_3	H	260° (DMF + water)	40%
6	$N(CH_3)_2$	6—CH_3	H	265° (methanol)	55%
7	$N(CH_3)_2$	6—$SO_2N(CH_3)_2$	H	214° (methanol)	50%
8		H	H	230° (DMF)	57%
9		H	H	164°(methanol-water)	68%
10		6—CF_3	H	174° (benzene) (hydrochloride: F = 250° (dec.)	40%

The intermediate products, identified in the following Table by the values assigned to the symbols used in formula II, may analogously be prepared

	X′	Y′	melting point (solvent of re-crystallisation)	Yield
$N(CH_3)_2$	6—Cl	H	118° (methanol)	84%
$N(CH_3)_3$	4—CF_3	H	119—120° (benzene)	90%
$N(CH_3)_2$	4—CH_3	H	142° (methanol)	75%
$N(CH_3)_2$	6—OCH_3	H	128° (methanol)	
$N(CH_3)_2$	6—NO	H	173° (acetone)	92%
$N(CH_3)_2$	4—$SO_2N(CH_3)_2$	H	177° (methanol + water)	87%

	X′	Y′	melting point (solvent of re-crystallisation)	Yield
	H	H	163° (acetone)	82%
	H	H	128° (acetone)	60%
	4—Cl	H	128° (isopropanol)	90%
	4—CF_3	H	hydrochloride 200—210° water decomp. (DMF)	60%

Example 11

6-trifluoromethylindole-3-carboxylic acid 1-(2-methoxy-phenyl)-4-piperazide

The compound 2 - (2 - nitro - 4 - trifluoromethyl - phenyl) - 2 - cyanoacetic acid 1 - (2-methoxyphenyl) - 4 - piperazide (9 g; 0.02 mol) in 100 ml of dimethylformamide is hydrogenated in the presence of 4 g of palladised carbon (10% palladium) at 50 atmospheres pressure of hydrogen at ambient temperature for 2 hours and then at 80° for 4 hours. After filtering to remove the catalyst, the filtrate is diluted with three times its volume of water to induce crystallisation of the piperazide: there is obtained 5 g (yield 62%) of pure product melting at 211—212°. Recrystallisation of this product from methoxymethanol (3 ml for 1 g) does not change the melting point.

The piperazide used as starting material is obtained as follows:

1 - cyanoacetyl - 4 - (2 - methoxyphenyl)-piperazine melting point 126° is prepared by reacting at 20°, for a week, 1 - (2 - methoxyphenyl) - piperazine with ethyl cynanoacetate in the presence of sodium ethylate and crystallising the product from benzene. The 1 - cyanoacetyl - 4 - (2 - methoxyphenyl) - piperazine (10 g; 0.04 mol) is converted to its sodium derivative by means of 2 g (0.08 mol) of sodium hydride in 100 ml. of dimethylformamide. There is then added, little by little, 9 g (0.04 mol) of 2 - nitro - 4 - trifluoromethyl - chlorobenzene in 20 ml of dimethylformamide, while maintaining the temperature at 20° and then continuing to stir the mixture at that temperature for 4 hours. The product is filtered, the filtrate diluted with 300 ml of water and then aqueous hydrochloric acid to obtain a pH of 3 to 4. The piperazide crystallises. It is separated, dried and recrystallised from 50 ml methanol. There is thus obtained 12 g (yield 70%) of pure piperazide, melting at 125—126°.

Example 12

6-fluoroindole-3-carboxylic acid 1-methyl-4-piperazide

The hydrochloride of 2 - (2 - nitro - 4-fluorophenyl) - 2 - cyanoacetic acid 1 - methyl-4 - piperazide (17.1 g; 0.05 mol) (mixed into 3 g of sodium chloride) in 100 ml of dimethylformamide is hydrogenated, at 50 atmospheres pressure, in the presence of 4 g. of palladised carbon (10% palladium) for 1 hour at ambient temperature and then at 80° for 4 hours. After filtering to remove the catalyst, the filtrate is evaporated down under vacuum, the residue taken up by 50 ml of a solution of 2 M potassium carbonate (0.1 mol) to liberate the base. This crystallises: it is separated, washed with water and dried under vacuum. There is thus obtained 7 g (yield 54%) of pure piperazide, melting at 192°. Recrystallisation of this product from methanol (4 ml per 1 g) does not alter the melting point.

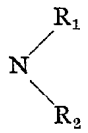
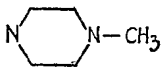
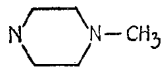
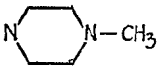
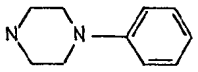
The piperazide used as starting material may be produced as follows:

1 cyanoacetyl - 4 - methylpiperazine (16.8 g; 0.01 mol) is converted to its sodium derivative by 0.5 g (0.2 mol) of sodium hydrate, in 150 ml of dimethylformamide. There is added, little by litttle, 16 g (0.1 mol) of 2,5-difluoronitrobenzene (prepared by the method of F. Swartz, Bull. Academic Royale de Belgique, (1913), p. 227) in 25 ml of dimethylformamide, maintaining the temperature at 20° and continuing the stirring of the mixture,

at that temperature, for 20 hours. The mixture is filtered and there is added to the filtrate a solution of hydrochloric acid in ether to obtain a clearly acid pH, and then anhydrous ether. The resulting precipitate is separated and washed, with ether. There is thus recovered 43 g (yield 97%) of the hydrochloride of the piperazide comprising 3.5 g of NaCl. This product may be used, without further purification for the hydrogenation.

Examples 13—16

By operating similarly the compounds identified in the following table, by the values of the symbols in formula 1, are obtained.

Ex.		X	Y	melting point solvent of recrystallisation	Yield
13		5—OCH_3	H	(without melting point) NMR in $CDCl_3$ Shift: CH_3 (of piperazide) 2.33 ppm CH_3 (of methoxy) 3.81 ppm CH_2 (near CO in the piperazine nucleus) 3.80 ppm CH_2 (far from CO in the piperazine nucleus) 2.45 ppm H (of the indole NH) 10.4 ppm monopicrate 255—256° (methoxyethanol)	60%
14		6—OCH_3	H	180°—182° (dimethylformamide + water)	53%
15		6—$SO_6N(CH_3)$	H	225—226° (chloroform)	45%
16		6—CF_3	H	240° (benzene)	50%

There may be analogously prepared the hydrochlorides of

2 - (2 - nitro - 5 - methoxyphenyl) - 2-cyanoacetic acid 1 - methyl - 4 - piperazide (Example 13)

2 - (2 - nitro - 5 - methoxyphenyl) - 2-cyanoacetic acid 1 - methyl - 4 - piperazide (Example 14)

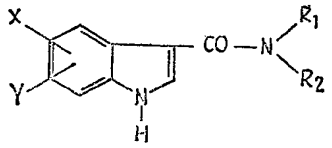
2 - (2 - nitro - 4 - dimethylsulphamoylphenyl) - 2 - cyanoacetic acid 1 - methyl-4 - piperazide (Example 15)

2 - (2 - nitro - 4 - trifluoromethylphenyl) 2 - cyanoacetic acid 1 - phenyl - 4-piperazide (M. Pt. 115—120°) (Example 16)

serving as intermediates.

WHAT WE CLAIM IS:—

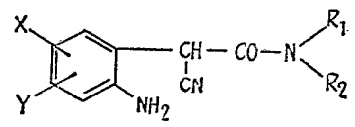
1. A process for the production of indole 3-carboxylic acid derivatives of the formula I:—



I

wherein R_1 and R_2 taken separately are the same or different and are hydrogen atoms or substituted or unsubstituted alkyl, aralkyl or aryl groups, and taken together with the nitrogen atom to which they are linked form a 5, 6 or 7 membered heterocyclic ring system which optionally may include a second hetero atom, and X and Y are the same or different and represent hydrogen atoms or halogen

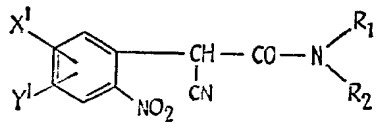
atoms, aralkoxy groups, trifluoromethyl, hydroxyl or amino groups or carboxylic or sulphonic acid groups or their functional derivatives, the said process comprising subjecting to hydrogenolysis a 2 - (2 - aminophenyl) - 2-cyanoacetic acid derivative of the formula III:—



III

where the symbols have the meanings assigned to them above.

2. A process according to claim 1 wherein a compound of the formula II



II

where R_1 and R_2 have the meanings assigned to them in claim 1 and X^1 and Y^1 have the values assigned to X and Y as defined in claim 1 or may additionally represent nitro groups, is reduced to form a derivative of formula III as set forth in claim 1 and the said compound of formula III is subjected to hydrogenolysis.

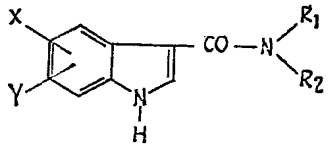
3. A process according to claim 1 or 2 wherein the hydrogenolysis is effected by treatment with hydrogen in the presence of a hydrogenation catalyst.

4. A process according to any of claims 1—3 wherein the hydrogenolysis is effected at a temperature of 50 to 150°C.

5. A process according to claim 2 wherein the reduction of a derivative of formula II to form a derivative of formula III is effected by catalytic hydrogenation at a temperature below 50°C.

6. A process according to claim 1 or 2 substantially as hereinbefore described with reference to any one of the foregoing specific Examples 1 to 16.

7. An indole-3-carboxylic acid derivative of formula I



(I)

wherein R_1, R_2, X and Y are as defined in claim 1 with the proviso that X and Y may not both be hydrogen except when R_1 and R_2 taken together represent a group of the formula $—(CH_2)_n—$ wherein n is an integer from 4 to 6.

8. A compound according to claim 7 selected from the dimethylamides of

6-trifluoromethyl	—	indole-3-carboxylic acid
6-methyl	—	" " " "
6-methoxy	—	" " " "
6-amino	—	" " " "
6-dimethylsulphamoyl	—	" " " "

the pyrrolidide and piperidide of indole-3-carboxylic acid, and the anilide of 6-trifluoromethylindole-3-carboxylic acid.

9. The compound 6 - trifluoromethylindole-3 - carboxylic acid 1 - methyl - 4 - piperazide.

10. The compound 6 - trifluoromethylindole - 3 - carboxylic acid 1 - (2 - methoxyphenyl) - 4 - piperazide.

11. The compound 6 - fluoroindole - 3-carboxylic acid 1 - methyl - 4 - piperazide.

12. The compound 5 - methoxyindole - 3-carboxylic acid 1 - methyl - 4 - piperazide.

13. The compound 6 - methoxyindole - 3-carboxylic acid 1 - methyl - 4 - piperazide.

14. The compound 6 - dimethylsulphamoylindole - 3 - carboxylic acid 1 - methyl - 4-piperazide.

15. The compound 6 - trifluoromethylindole - 3 - carboxylic acid 1 - phenyl - 4-piperazide.

16. A therapeutic composition comprising a compound as defined in claim 7 together with a pharmaceutically acceptable solid or liquid diluent.

17. A therapeutic composition according to

claim 16 wherein the active compound is a compound as defined in any of claims 9—15.

18. A herbicidal composition comprising a compound as defined in claim 7 together with a surface-active agent.

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